Complete Summary

GUIDELINE TITLE

Adalimumab, etanercept and infliximab for ankylosing spondylitis.

BIBLIOGRAPHIC SOURCE(S)

National Institute for Health and Clinical Excellence (NICE). Adalimumab, etanercept and infliximab for ankylosing spondylitis. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 May. 47 p. (Technology appraisal guidance; no. 143).

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references drug(s) for which important revised regulatory and/or warning information has been released.

- May 1, 2008, Enbrel (etanercept): Amgen and Wyeth Pharmaceuticals informed healthcare professionals of changes to the BOXED WARNING section of the prescribing information for Enbrel regarding the risk of serious infections, including bacterial sepsis and tuberculosis, leading to hospitalization or death. The ADVERSE REACTIONS section of the label was updated to include information regarding global clinical studies and the rate of occurrence of tuberculosis in patients treated with Enbrel.

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

Ankylosing spondylitis

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Family Practice
Internal Medicine
Rheumatology

INTENDED USERS

Advanced Practice Nurses
Nurses
Physician Assistants
Physicians

GUIDELINE OBJECTIVE(S)

To evaluate the clinical effectiveness and cost-effectiveness of adalimumab, etanercept, and infliximab for the treatment of ankylosing spondylitis

TARGET POPULATION

Adult patients with active ankylosing spondylitis

INTERVENTIONS AND PRACTICES CONSIDERED

1. Adalimumab or etanercept
2. Regular monitoring of the response to treatment

Note:

- Infliximab was considered but not recommended
- Prescription of an alternative tumour necrosis factor-alpha (TNF-alpha) inhibitor is not recommended in patients who have either not achieved an adequate initial response to treatment with adalimumab or etanercept, or who experience loss of the initially adequate response during treatment.

MAJOR OUTCOMES CONSIDERED

- Clinical effectiveness
    - Pain and other symptoms
    - Functional capacity (e.g., Bath Ankylosing Spondylitis Functional Index [BASFI])
    - Disease activity (e.g., Bath Ankylosing Spondylitis Disease Activity Index [BASDAI])
    - Adverse effects of treatment
    - Disease progression (e.g., BASDAI)
    - Health related quality of life (e.g., short form [SF]-36 or ankylosing spondylitis quality of life [ASQoL])
- Cost-effectiveness

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by Liverpool Reviews and Implementation Group, University of Liverpool (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Search Strategy

The search incorporated a number of strategies. Search terms for electronic databases included a combination of index terms for ankylosing spondylitis (AS) and free text words for the technologies involved (generic and trade names of the drugs).

The following electronic databases were searched for relevant published literature for the period to November 2005:

- CDSR (Cochrane Database of Systematic Reviews)
- CENTRAL (Cochrane Central Register of Controlled Trials)
- DARE (Database of Abstracts of Reviews of Effectiveness)
- EMBASE
- Health Technology Assessment database
- ISI Web of Science- Proceedings (Index to Scientific & Technical Proceedings)
- ISI Web of Science- Science Citation Index Expanded
- MEDLINE
- NHS EED (National Health Service Economic Evaluation Database).

Details of the search strategies and the number of records retrieved for each search are provided in Appendix 1 of the Assessment Report (see the "Availability of Companion Documents" field).

Reference lists of included studies and industry submissions were searched to identify other relevant studies of clinical effectiveness.

Handsearching of three rheumatology conference abstracts (up to 31 January 2005) was conducted for:

- British Society of Rheumatology 2003, 2004, 2005
- EULAR (Annual European Congress of Rheumatology) 2003, 2004, 2005
- American College of Rheumatology 2003, 2004, 2005.

All the references were initially exported to an *EndNote* bibliographic database, Thomson ISI ResearchSoft, Cal., USA. From this EndNote library, references were then uploaded to TrialStat! SRS 3.0 web-based systematic review system (TrialStat! Corporation, Ontario, Canada) for deduplication and application of inclusion/exclusion criteria (see below).

Selection of Evidence

The records identified in the electronic searches were assessed for inclusion in two stages.

Initial Screening – Electronic (SRS)

Using the SRS web-based systematic reviewing system each record (title and, if available, abstract in electronic form) was screened for inclusion in the clinical review by two reviewers operating independently.

Full text versions of all records passing (i.e., not excluded) the initial screening process were obtained to permit more detailed assessment. A table summarising the initial screening of search results is given in Appendix 1 of the Assessment Report (see the "Availability of Companion Documents" field).

Study Selection and Categorisation – Full Text

Full text reports of the selected records were obtained and assessed independently by at least two reviewers for inclusion. The inclusion/exclusion assessment of each reviewer was recorded on a pre-tested, standardised (paper) form.

Data on levels of agreement between reviewers is available from the Assessment Group upon request. A table summarising the selection and inclusion of studies is provided in Appendix 1 of the Assessment Report (see the "Availability of Companion Documents" field).

Inclusion Criteria

The following inclusion criteria were applied to evidence sources identified in the Assessment Group search.

Study Design(s)

- Randomised controlled trials (RCTs)
- Non-RCTs (such as non-randomised Phase I trials) in the absence of sufficient RCT-based data

Patient Population

- Etanercept and infliximab - adults with active AS whose disease has responded inadequately to conventional therapy.
- Adalimumab - adults with active AS.

Interventions

- Adalimumab, etanercept or infliximab plus conventional management

Comparators

- Conventional management (such as non-steroidal anti-inflammatory drugs [NSAIDs], physiotherapy, disease-modifying anti-rheumatic drugs [DMARDs] and corticosteroids) without anti-tumour necrosis factor (TNF) alpha therapy.

Outcomes

- Pain and other symptoms
- Functional capacity **(**e.g., Bath Ankylosing Spondylitis Functional Index [BASFI])
- Disease activity (e.g., Bath Ankylosing Spondylitis Disease Activity Index [BASDAI])
- Adverse effects of treatment
- Disease progression (e.g., BASDAI)
- Health related quality of life (e.g., short form [SF]-36 or ankylosing spondylitis quality of life [ASQoL])

Exclusion Criteria

Randomised studies were excluded if they:

- Provided only unplanned, interim findings
- Provided data on only a sub-group of the enrolled patients
- Were continuing to recruit patients
- Where patients numbers treated with specific intervention (i.e., adalimumab, etanercept or infliximab) or disease status (i.e., active AS) cannot be determined.

Cost-Effectiveness

A systematic search of the economic evidence concerning anti-TNF alpha therapy for the treatment of AS was conducted. The aim was to identify published cost-effectiveness studies of anti-TNF alpha therapy for the treatment of AS versus any other conventional therapy.

Using the search strategy "ankylosing spondylitis and cost" (refer to Table 3-1 of the Assessment Group report [see the "Availability of Companion Documents" field]), 166 papers were identified. Of these 54 duplicates were discarded, and the remaining 112 were selected.

Selection of Evidence

Full text reports of the selected records were obtained and assessed independently by two reviewers for inclusion. The inclusion/exclusion assessment of each reviewer was recorded on a pre-tested, standardised (paper) form.

Any disagreements for inclusion of cost-effectiveness studies were resolved by discussion.

Inclusion Criteria

The following criteria had to be met in order for the evidence source to be considered in the review of cost-effectiveness.

Study Design

- Full economic evaluations that compared two or more options and considered both costs and consequences including: cost-effectiveness analysis, cost-utility analysis, cost-benefit analysis, and cost minimisation analysis.

Population

- Etanercept and infliximab - adults with active AS whose disease has responded inadequately to conventional therapy.
- Adalimumab - adults with active AS.

Intervention

- Adalimumab, etanercept or infliximab plus conventional management

Comparators

- Conventional management without anti-TNF alpha or placebo
- Adalimumab, etanercept or infliximab plus conventional management

Health Outcomes in an Economic Framework

- Incremental cost per quality adjusted life year gained.

- Disease specific measures such as: assessment of ankylosing spondylitis (ASAS) 20 responder, ASAS partial responder, disease controlling anti-rheumatic treatment (DCART) 20 responder, BASDAI scores, BASFI scores.

Exclusion Criteria

Reports were excluded from the review of economic evaluations if they were:

- Rheumatoid arthritis studies
- Not full economic evaluations
- The interventions did not include adalimumab, etanercept, or infliximab

NUMBER OF SOURCE DOCUMENTS

Clinical Effectiveness

Nine RCTs were included in the clinical review.

Cost-Effectiveness

- Published literature: 6 studies (2 full papers and 4 abstracts)
- Three manufacturers' submissions

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis
Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Clinical Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this appraisal and prepare an assessment report. The assessment report for this technology appraisal was prepared by Liverpool Reviews and Implementation Group, University of Liverpool (see the "Availability of Companion Documents" field).

Clinical Effectiveness

Data Abstraction

Data extraction for the review of clinical effectiveness was carried out by three reviewers. Data were abstracted by one reviewer into pre-tested data extraction forms created within the *Access* database application, Microsoft Corporation, and then checked for accuracy by a second reviewer.

Data presented from multiple reports of single trials were extracted onto a single data extraction record.

Quality Assessment

Two reviewers independently evaluated the included studies for methodological quality (utilising forms created in Access) using criteria based on the Centre for Reviews and Dissemination, Report 4 (refer to Appendix 2 of the Assessment Report [see the "Availability of Companion Documents" field]). Any discrepancies in quality grading were resolved through discussion.

Data Analysis

Abstracted data were presented as tables and, if appropriate, included in the meta-analysis.

Data in the form of relative risks (RR) and 95% confidence intervals (CI) were analysed using the Mantel-Haenszel method, fixed-effect model provided by the *RevMan Analyses 1.0* application within *RevMan 4.2.* For continuous outcomes, weighted mean differences (WMD) were analysed, using a fixed-effect model and the same analytical software.

Heterogeneity was tested by the chi-squared test and the I^2 statistic was obtained to describe the proportion of the variability using *RevMan Analyses 1.0.* Where quantitative heterogeneity was indicated, analysis using a random-effects model was conducted for comparison with results of fixed-effect based analysis. Results of the meta-analysis should be considered as being based on fixed-effect model unless stated otherwise.

Refer to section 4 of the Assessment Report (see the "Availability of Companion Documents" field) for more information on methods used to analyze clinical effectiveness.

Cost-Effectiveness

Data Abstraction

Data from the included economics studies were abstracted into structured tables by one reviewer and then checked for accuracy by a second reviewer.

Quality Assessment

Two reviewers independently evaluated the included economics studies for methodological quality using criteria based on British Medical Journal (BMJ)

Guidelines for authors and peer reviewers of economic submissions (refer to Appendix 2 of the Assessment Group report [see the "Availability of Companion Documents" field]). Any discrepancies in quality grading were resolved through discussion.

Data Synthesis

Data are presented in structured tables and described within the appropriate section of the Assessment Report (see the "Availability of Companion Documents" field).

Refer to section 6 of the Assessment Report (see the "Availability of Companion Documents" field) for information about the manufacturers' models.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Considerations

Technology appraisal recommendations are based on a review of clinical and economic evidence.

Technology Appraisal Process

The National Institute for Health and Clinical Excellence (NICE) invites 'consultee' and 'commentator' organisations to take part in the appraisal process. Consultee organisations include national groups representing patients and carers, the bodies representing health professionals, and the manufacturers of the technology under review. Consultees are invited to submit evidence during the appraisal and to comment on the appraisal documents.

Commentator organisations include manufacturers of the products with which the technology is being compared, the National Health Service (NHS) Quality Improvement Scotland and research groups working in the area. They can comment on the evidence and other documents but are not asked to submit evidence themselves.

NICE then commissions an independent academic centre to review published evidence on the technology and prepare an 'assessment report'. Consultees and commentators are invited to comment on the report. The assessment report and the comments on it are then drawn together in a document called the evaluation report.

An independent Appraisal Committee then considers the evaluation report. It holds a meeting where it hears direct, spoken evidence from nominated clinical experts, patients and carers. The Committee uses all the evidence to make its first recommendations, in a document called the 'appraisal consultation document'

(ACD). NICE sends all the consultees and commentators a copy of this document and posts it on the NICE website. Further comments are invited from everyone taking part.

When the Committee meets again it considers any comments submitted on the ACD; then it prepares its final recommendations in a document called the 'final appraisal determination' (FAD). This is submitted to NICE for approval.

Consultees have a chance to appeal against the final recommendations in the FAD. If there are no appeals, the final recommendations become the basis of the guidance that NICE issues.

Who is on the Appraisal Committee?

NICE technology appraisal recommendations are prepared by an independent committee. This includes health professionals working in the NHS and people who are familiar with the issues affecting patients and carers. Although the Appraisal Committee seeks the views of organisations representing health professionals, patients, carers, manufacturers and government, its advice is independent of any vested interests.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

Adalimumab – Manufacturer's (Abbot Laboratories Ltd) Model

The manufacturer's economic evaluation – structured as a patient-based transition-state model – compared the use of adalimumab plus non-steroidal anti-inflammatory drugs (NSAIDs) versus treatment with NSAIDs alone. This model incorporated patient-level data from the Canadian ankylosing spondylitis and ATLAS randomised controlled trials (RCTs), and aimed to simulate treatment decisions based on the British Society for Rheumatology (BSR) guidelines. The trial populations included patients who would not have met BSR eligibility criteria; for example, patients who were intolerant of, or whose ankylosing spondylitis had responded inadequately to, fewer than two NSAIDs.

The model consisted of two components. The first used short-term trial data (first 48 weeks). The second component simulated long-term outcomes for responders for up to 30 years.

In the base-case, the incremental cost-effectiveness ratio (ICER) over a 30-year time horizon was about 23,000 pounds sterling per quality adjusted life year (QALY) gained. Univariate sensitivity analyses on a number of parameters including annual discontinuation rates were undertaken; ICERs varied from 18,000 pounds sterling per QALY gained to around 27,000 pounds sterling per QALY gained (over 30 years).

Etanercept – Manufacturer's (Wyeth Pharmaceuticals) Model

The manufacturer's model compared the use of etanercept plus NSAIDs with NSAIDs alone. The model generated a hypothetical patient population based on patient-level data from two RCTs and an open-label extension. The principal RCT evidence used in the model was drawn from a single study (n = 356). The time horizon was up to 25 years.

In the base-case, the ICER was reported to be around 13,200 pounds sterling over a 25-year time horizon. A number of univariate sensitivity analyses were undertaken. When a utility model based on short-form (SF)-36 data was used, ICERs were found to vary between 17,000 pounds sterling and 70,000 pounds sterling per QALY gained. Probabilistic sensitivity analysis indicated that over a 25-year time period, etanercept has an 88% probability of being cost effective at a threshold willingness to pay of 15,000 pounds sterling.

Infliximab – Manufacturer's (Schering-Plough Ltd) Model

The manufacturer's model is based on a combined decision tree and Markov chain structure, and compares infliximab versus 'standard therapy'. Two analyses were described, one based on the 24-week outcomes of the ASSERT trial and the other on a smaller study of up to 12 weeks. The placebo groups in these studies were assumed to have received standard therapy as these studies allowed the concomitant use of NSAIDs.

In the base-case, the reported ICERs in the original submission were under 20,000 pounds sterling. However, this was based on an inaccurate model, which in part allowed patients who withdrew from infliximab treatment to avoid being assigned an 'off-treatment' disease progression. On correcting this error, the manufacturer reported base-case 70-year ICERs of approximately 27,000 pounds sterling to 28,000 pounds sterling per QALY gained (depending on which of the two studies is used to inform the calculation). In contrast, the Assessment Group found that, on correcting the model within an Excel replica, the lifetime ICERs were between 41,000 pounds sterling and 50,000 pounds sterling per QALY gained. The manufacturer also reported corrected ICERs for the scenario in which disease progression while on treatment is assumed to be 50% of natural history (that is, 0.035 units per year), and the ICERs rise to between 34,000 pounds sterling and 35,000 pounds sterling per QALY gained.

The Assessment Group Model

The Assessment Group examined the use of adalimumab, etanercept and infliximab compared with 'conventional treatment'. 'Conventional treatment' was defined in terms of the placebo arms of two adalimumab RCTs. The group explored the cost effectiveness of these interventions over the short term (1 year) and over a time horizon of up to 20 years.

Under base-case assumptions, from week 30 onwards it was assumed that spontaneous recovery without treatment would occur at a rate of 17.1% as identified in the patient-level analysis of two adalimumab RCTs supplied in the Abbott submission. This assumption was explored in univariate and multivariate sensitivity analyses. In univariate sensitivity analyses, in which it was assumed there was no spontaneous recovery in the placebo arm, the ICERs for adalimumab and etanercept over a 20-year time horizon decreased from 92,000 pounds

sterling (base-case) to 57,000 pounds sterling. The ICER for infliximab decreased from 168,000 pounds sterling (base-case) to 109,000 pounds sterling.

Univariate and multivariate sensitivity analyses were undertaken. Multivariate sensitivity analyses identified scenarios in which adalimumab/etanercept could be considered cost effective, with ICERs ranging from 12,000 pounds sterling to 118,000 pounds sterling. Important factors influencing the long-term cost effectiveness of these two drugs included assumptions about spontaneous recovery, withdrawal rate from treatment and the Bath Ankylosing Spondylitis Functional Index (BASFI) progression rate. Multivariate sensitivity analyses on the infliximab results identified no scenario in which the ICER dropped below 35,000 pounds sterling.

Further Analysis by the Decision Support Unit (DSU)

Following consultation on the submissions from the three manufacturers and the Assessment Group, the Committee requested additional analysis to be carried out by the Decision Support Unit to identify reasons for the large differences in the cost-effectiveness results and to determine whether the differences in the results still existed when an agreed set of common parameter values were included.

Using a common set of parameter values in the manufacturers' models and applying the assumption of no disease progression after 1 year for tumour necrosis factor (TNF)-alpha inhibitor treatment responders to the Assessment Group's model, gave revised results for adalimumab/etanercept of 30,000 pounds sterling per QALY gained, down from 42,000 pounds sterling per QALY gained. If no disease progression was assumed for adalimumab or etanercept after 20 weeks, the ICER becomes 22,000 pounds sterling per QALY gained. The equivalent ICER for infliximab if no disease progression was assumed after 20 weeks was 49,000 pounds sterling per QALY gained. The DSU commented that the assumption of zero response in the placebo arm was a favourable one. If this assumption is not made, the ICERs for the Assessment Group's model move from 30,000 pounds sterling per QALY gained to 47,000 pounds sterling per QALY gained if no disease progression is assumed after the first year, and from 22,000 pounds sterling per QALY gained to 31,000 pounds sterling per QALY gained, if no disease progression is assumed after the first 20 weeks.

Consideration of the Evidence

The Committee considered the evidence for the cost effectiveness of TNF-alpha inhibitors.

The Committee considered the DSU's assumption of stable Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and BASFI after 20 weeks to be appropriate in this context. The resulting ICER of 22,000 pounds sterling per QALY gained calculated by the DSU for adalimumab and etanercept using the Assessment Group model, in which BASDAI and BASFI remain stable after 20 weeks, was also considered to be plausible in this context. The Committee noted that the ICER for infliximab, using the stable BASDAI and BASFI profiles, was 49,000 pounds sterling per QALY gained.

The Committee considered that the assumption around no spontaneous resolution of symptoms, equivalent to absence of a placebo response, was unlikely. It heard from the DSU that if a 17% response in the placebo arm was assumed (as in the original Assessment Group model) then the ICER of 22,000 pounds sterling per QALY gained would increase to 31,000 pounds sterling per QALY gained for etanercept and adalimumab. The Committee considered that these two figures represented a reasonable range of cost effectiveness based on the evidence. The equivalent figures for infliximab were 49,000 pounds sterling to 65,000 pounds sterling per QALY gained. Therefore, on balance, taking into account all of its previous assumptions, the Committee concluded that adalimumab and etanercept for the treatment of severe ankylosing spondylitis could be considered a cost-effective use of National health Service (NHS) resources in the context of achieving a continued response to treatment.

The Committee discussed the cost effectiveness of infliximab in further detail. Because the available evidence persuaded the Committee that infliximab was not cost effective in treating ankylosing spondylitis, it concluded that it could not recommend the use of infliximab simply on the basis of another treatment choice.

Refer to Section 4 of the original guideline document for details of the economic analyses provided by the manufacturers, the Assessment Group comments, and the Appraisal Committee considerations.

METHOD OF GUIDELINE VALIDATION

External Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Consultee organizations from the following groups were invited to comment on the draft scope, Assessment Report and the Appraisal Consultation Document (ACD) and were provided with the opportunity to appeal against the Final Appraisal Determination.

- Manufacturer/sponsors
- Professional/specialist and patient/carer groups
- Commentator organisations (without the right of appeal)

In addition, individuals selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups were also invited to comment on the ACD.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Adalimumab or etanercept are recommended as treatment options for adults with severe active ankylosing spondylitis only if all of the following criteria are fulfilled.

- The patient's disease satisfies the modified New York criteria for diagnosis of ankylosing spondylitis.

- There is confirmation of sustained active spinal disease, demonstrated by:
    - A score of at least 4 units on the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) **and**
    - At least 4 cm on the 0 to 10 cm spinal pain visual analogue scale (VAS).

  These should both be demonstrated on two occasions at least 12 weeks apart without any change of treatment.

- Conventional treatment with two or more non-steroidal anti-inflammatory drugs taken sequentially at maximum tolerated or recommended dosage for 4 weeks has failed to control symptoms.

When using BASDAI and spinal pain VAS scores to inform conclusions about whether or not sustained active spinal disease is present, healthcare professionals should be mindful of the need to secure equality of access to treatment for patients with disabilities and patients from different ethnic groups. There are circumstances in which it may not be appropriate for healthcare professionals to use a patient's BASDAI and spinal pain VAS scores to inform their conclusion about the presence of sustained active spinal disease. These are:

- Where the BASDAI or spinal pain VAS score is not a clinically appropriate tool to inform a clinician's conclusion on the presence of sustained active spinal disease because of a patient's learning or other disabilities (for example, sensory impairments) or linguistic or other communication difficulties

  or

- Where it is not possible to administer the BASDAI or spinal pain VAS questionnaire in a language in which the patient is sufficiently fluent for it to be an appropriate tool to inform a conclusion on the presence of sustained active spinal disease, or there are similarly exceptional reasons why use of a patient's BASDAI or spinal pain VAS score would be an inappropriate tool to inform a conclusion on the presence of sustained active spinal disease in that individual patient's case.

In such cases, healthcare professionals should make use of another appropriate method of assessment, which may include adapting the use of the questionnaire to suit the patient's circumstances.

The same approach should apply in the context of a decision about whether to continue the use of the drug in accordance with the two following paragraphs.

It is recommended that the response to adalimumab or etanercept treatment should be assessed 12 weeks after treatment is initiated, and that treatment should be only continued in the presence of an adequate response as defined below.

For the purposes of this guidance, an adequate response to treatment is defined as a:

- Reduction of the BASDAI score to 50% of the pre-treatment value or by 2 or more units **and**
- Reduction of the spinal pain VAS by 2 cm or more.

Patients who have experienced an adequate response to adalimumab or etanercept treatment, as defined above, should have their condition monitored at 12-week intervals. If the response to treatment, is not maintained, a repeat assessment should be made after a further 6 weeks. If at this 6-week assessment the response defined above has not been maintained, treatment should be discontinued.

For patients who have been shown to be intolerant of adalimumab or etanercept before the end of the 12-week initial assessment period, the other one of this pair of TNF-alpha inhibitor treatments is recommended as an alternative treatment.

Prescription of an alternative TNF-alpha inhibitor is not recommended in patients who have either not achieved an adequate initial response to treatment with adalimumab or etanercept, as defined above, or who experience loss of the initially adequate response during treatment.

It is recommended that the use of adalimumab or etanercept for severe active ankylosing spondylitis should be initiated and supervised only by specialist physicians experienced in the diagnosis and treatment of this condition.

Infliximab is not recommended for the treatment of ankylosing spondylitis.

Patients currently receiving infliximab for the treatment of ankylosing spondylitis should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of evidence supporting the recommendations is not specifically stated.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate use of tumour necrosis factor (TNF)–alpha inhibitors (adalimumab, etanercept, and infliximab) in patients with ankylosing spondylitis

POTENTIAL HARMS

- Common adverse events reported during *adalimumab* therapy include injection-site reactions and infections. Uncommon adverse events included non-serious allergic reactions. Before treatment begins all patients must be evaluated for both active and inactive (latent) tuberculosis infection.
- The most frequent adverse events reported during *etanercept* therapy include injection-site reactions, infections and in some instances allergic reactions.
- The most common adverse events reported during *infliximab* therapy include acute infusion-related reactions, infections, delayed hypersensitivity reactions, and in some instances allergic reactions.

The summary of product characteristics (SPC) specifies a number of uncommon but serious adverse events that may be related to the immunomodulatory activity of these drugs.

For full details of side effects and contraindications, see the SPC.

CONTRAINDICATIONS

CONTRAINDICATIONS

- *Adalimumab* is contraindicated in patients with moderate to severe heart failure, active tuberculosis or other active infections.
- *Etanercept* is contraindicated in people with sepsis or risk of sepsis, active infections like tuberculosis, and hypersensitivity to the active substance or excipients.
- *Infliximab* is contraindicated in people with moderate or severe heart failure, active tuberculosis and, before treatment is initiated, people must be screened for both active and inactive tuberculosis.

For full details of side effects and contraindications, see the summary of product characteristics (SPC).

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- This guidance represents the view of the Institute, which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. The guidance does not, however, override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

- The Healthcare Commission assesses the performance of National Health Service (NHS) organizations in meeting core and developmental standards set by the Department of Health in "Standards for Better Health" issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by the National Institute for Health and Clinical Excellence (NICE) technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.
- "Healthcare Standards for Wales" was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 which requires Local Health Boards and NHS Trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.
- NICE has developed tools to help organisations implement this guidance (listed below). These are available on the NICE Web site (see also the "Availability of Companion Documents" field).
    - Costing template incorporating a costing report to estimate the savings and costs associated with implementation.
    - Audit support for monitoring local practice.

IMPLEMENTATION TOOLS

Audit Criteria/Indicators
Patient Resources
Quick Reference Guides/Physician Guides

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

National Institute for Health and Clinical Excellence (NICE). Adalimumab, etanercept and infliximab for ankylosing spondylitis. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 May. 47 p. (Technology appraisal guidance; no. 143).

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2008 May

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National Institute for Health and Clinical Excellence (NICE)

GUIDELINE COMMITTEE

Appraisal Committee

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) format from the National Institute for Health and Clinical Excellence (NICE) Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following are available:

- Adalimumab, etanercept and infliximab for ankylosing spondylitis. Quick reference guide. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 May. 2 p. (Technology appraisal 143). Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.
- Adalimumab, etanercept and infliximab for ankylosing spondylitis. Costing template and report. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 May. Various p. (Technology appraisal 143). Available in Portable Document Format (PDF) from the NICE Web site.
- Adalimumab, etanercept and infliximab for ankylosing spondylitis. Audit support. London (UK): National Institute for Health and Clinical Excellence

(NICE); 2008. 10 p. (Technology appraisal 143). Available in Portable Document Format (PDF) from the NICE Web site.

- Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis. Assessment Report. London (UK): National Institute for Health and Clinical Excellence (NICE); 2006. 194 p. (Technology appraisal 143). Available in Portable Document Format (PDF) from the NICE Web site.

Print copies: Available from the National Health Service (NHS) Response Line 0870 1555 455. ref: N1570. 11 Strand, London, WC2N 5HR.

PATIENT RESOURCES

The following is available:

- Adalimumab, etanercept and infliximab for ankylosing spondylitis. Understanding NICE guidance. Information for people who use NHS services. London (UK): National Institute for Health and Clinical Excellence (NICE); 2008 May. 4 p. (Technology appraisal 143). Available in Portable Document Format (PDF) from the National Institute for Health and Clinical Excellence (NICE) Web site.

Print copies: Available from the NHS Response Line 0870 1555 455. ref: N1571. 11 Strand, London, WC2N 5HR.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

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